REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Initially, Applicants wish to express their appreciation to the Examiner for his courtesy and helpful suggestions made to the Applicant's representative during the interview on December 13, 2006.

Claims 21-28, 31-32, 35-36 and 39-40 are cancelled without prejudice.

Claims 29-30, 33-34 and 37-38 have been amended along the lines suggested by the Examiner during the interview. Specifically, the claims have been amended to recite "a sustained release preparation" as suggested by the Examiner, to distinguish over the Lerner burst type preparation. The product claims have been revised to remove the process language as suggested by the Examiner. The method claims have been amended to recite more clear process steps. Other amendments have been effected to more particularly point out and distinctly claim the subject matter of this invention. Support for the amendments to claim 29 are found in the specification at page 8, line 7 to page 9, line 5 and the paragraph bridging pages 11-12 of the specification. The amendments to claim 30 are supported by the specification at page 10, lines 9-25. The amendments to claim 33 are supported as indicated above and also on page 7, lines 1-4 of the specification. The amendments to claim 34 are indicated above.

Turning to the Official Action, there is a single ground of rejection. Claims 21-40 are rejected under 35 USC 103 as unpatentable over Lerner et al. This ground of rejection is respectfully traversed as applied to the amended claims.

In the Office Action, the Examiner suggested additional experiments to demonstrate the unexpected effects of the claimed invention. During the interview, additional experiments were discussed. There is submitted herewith a Supplemental Rule 132 Declaration of Mr. Shimono which is believed to address the deficiencies of the original Declaration.

1. The Examiner suggested that we add Ref. Preparation A, B, C, D and E at a:b of 3:7 and a:b of 1:1.

2. The Examiner suggested that we add Prepar. F, G, H, I, J, K and L using b: ethyl cellulose and b: Eudragit NE30D.

3. The Examiner tentatively suggested that we specify the thickness of the coating in the comparative examples. The Examiner also proposed that the claims be amended to recite a range of coating thickness.

4. The Examiner tentatively suggested that we specify the chitosan particle size in the comparative examples. The Examiner also proposed that the claims be amended to recite a range of chitosan particle sizes.

(1) Along with the Examiner's suggestion 1, Ref. preparations A, D and E at a:b of 3:7 and a:b of 1:1 were prepared along with the formulations disclosed in Examples 3, 7 and 8 of Lerner et al. as Ref. prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1), and E(3/7) and were compared with the Prepar. F, G, H, I, and J of the present invention (cf. Experiment 1A in Mr. Shimono's Supplemental Declaration).

Reference preparations (a:b = 1:1 or 3:7) corresponding to Ref. preparations B and C were not prepared, because Ref. preparations B and C are common to Ref. preparation A in the kind of the dispersed particles (calcium pectinate). Further it will be well assumed that those preparations will show the same or similar release profile in the light of the experimental results shown in Experiment 2A, wherein the release profile of the preparations were substantially not affected by the kinds of the water-insoluble polymers (even by using ethyl cellulose or Eudragit NE30D® instead of Eudragit RS®).

As the Examiner will see from said comparative experimental data, even when the ratio of (a):(b) was changed to 1:1 or 3:7, the preparations of Lerner et al. showed very rapid dissolution profile as the reference preparations A, B, C, D and F having the ratio of (a):(b) of 7:3. It is assumed that in the Ref. preparations, the tablets would be swollen with the 1st fluid and then disintegrated, by which the active ingredient was dissolved out very rapidly. On the other hand, in Prepar. F, G, H, I and J of the present invention with the claimed ratio of (a):(b) of 1:4 to 4:1, the coating of the tablets would not be swollen and the original tablet form was kept

for more than 8 hours, and thereby the active ingredient was dissolved out very gradually and can show excellent sustained release properties.

(2) Along with the Examiner's suggestion 2, the preparations of the present invention using b: ethyl cellulose and b:Eudragit NE30D® were prepared as Prepar. M, N and Prepar. O of the present invention and the release properties of the active ingredient were tested likewise (cf. Experiment 2A and Experiment 3A in Mr. Shimono's Supplemental Declaration).

As the Examiner will see from these experimental data, the Prepar. M and N and Prepar. O of the present invention using ethyl cellulose and Eudragit NE30D® as the water-insoluble polymer showed excellent sustained release properties as like as the Prepar. F, G, H, I and J of the present invention using other water-insoluble polymer, Eudragit RS® (cf. the Fig. 1A in Mr. Shimono's Supplemental Declaration as well as Fig. 1 to Fig. 3 in Mr. Shimono's former Declaration).

Thus, it has experimentally been proved that the preparations of the present invention can show the excellent sustained release properties in all cases using as the water-insoluble polymer Eudragit RS®, ethyl cellulose and Eudragit NE30D®.

(3) The Examiner tentatively suggested to specify the thickness of the coating in the comparative examples in the Examiner's suggestion 3. For all of the Ref. preparations of Lerner et. al. as well as preparations of the present invention experimented in this time the thickness of the coating was specified as shown in Fig. 1A, Fig. 2A and Fig. 3A of Mr. Shimono's Supplemental Declaration, wherein the thickness of the coating layer of the preparations is shown in the parenthesis after each preparation.

As seen from Fig. 1A, although Ref. Prepar. A(1/1), A(3/7), D(1/1), D(3/7), E(1/1),E(3/7) of Lerner et al. had a larger coating thickness of from 139 to 107 μm than that (100 μm) of the preparations of the present invention, the Ref. preparations of Lerner et al. dissolved more rapidly. This suggests that the dissolution profile of the preparations was almost not effected by thickness of the coating layer, but was effected much more by the kinds of the dispersed particles in the coating layer.

Lerner et al. mention as "Drug release is controlled by varying the following parameters; (1) size of the particulate matter; (2) thickness of the coating; (3) type of material forming the particulate matter; (4) ratio of particulate matter; and (5) water-insoluble film forming material." (cf. Lerner et al. USP 5,840,332, Col. 11, lines 51-55). However it has been found that as far as concerning at least the preparations of the present invention, among the above parameters, the parameter (3) type of material forming the particulate matter was the most important while other parameters such as (1) size of the particulate matter (the dispersed particle), (2) thickness of the coating film, (4) the ratio of the particulate matter, and (5) the kinds of the water-insoluble polymer were not such important parameters. It has been found by the present inventors that by coating a medicament-containing material with a coating solution wherein chitosan is dispersed in a water-insoluble polymer selected from Eudragit RS®, ethyl cellulose and Eudragit NE30D®, the preparations showed unexpectedly superior sustained release properties of the active medicament contained in the preparation when orally administered.

According to common knowledge in the field of pharmaceuticals, it may be generally said that "the thinner the coating in a medicament, the quicker the release of the active ingredient from the core material." Nevertheless, it is not necessarily correct regarding the preparation of the present invention with coating of the dispersed solution wherein chitosan powder is dispersed in a solution of a water-insoluble polymer, which was proved experimentally as mentioned above.

Thus, even from this viewpoint only, the present invention could have never been expected from the cited Lerner et al. reference.

Although the Examiner further proposed to recite a range of coating thickness in the amended claims, the Applicant respectfully disagrees because the thickness of the coating is not an essential parameter for the sustained release properties of the preparation of the present invention.

(4) The Examiner further tentatively suggested to specify the chitosan particle size in the comparative examples in the Examiner's suggestion 4. In Experiment 2A, the preparations having different particle sizes of chitosan were compared. That is, in Prepar. M and Prepar. N,

the chitosan powder to be dispersed in the water-insoluble polymer was the pulverized one (particle size, 6 μm) and the unpulverized one (particle size, 110 μm), respectively, and further both preparations had different thickness of the coating, i.e. 192 μm (Prepar. M) and 166 μm (Prepar. N). However, as is seen from the experimental results shown in Fig. 2A, the excellent release profiles were similar to each other.

Thus, it has been experimentally proved that the excellent sustained release properties of the preparations of the present invention are not substantially affected by the chitosan particle size or by the thickness of the coating.

Accordingly, even though the Examiner proposed to recite the chitosan particle size in the amended claims, the Applicant respectfully disagrees because it is not an essential parameter for the sustained release properties of the present invention.

As is clear from the above explanation based on the comparative experiments shown in Mr. Shimono's Supplemental Declaration as well as his former Declaration, the preparation of the present invention comprising a medicament-containing solid material and a water-insoluble coating film, wherein said coating film consisting essentially of a water-insoluble polymer selected from ethyl cellulose, Eudragit RS® and Eudragit NE30D® and a chitosan powder dispersed in said polymer, has superior release profile (sustained release properties) of the active ingredient contained in the medicament-containing solid material (core). Such excellent sustained release properties of the present preparation are not taught or suggested by the cited Lerner et al. reference.

Thus, it is respectfully submitted that the patentability of the present invention over the cited Lerner et al. reference is clear from the above explanation based on the comparative experiments. In view of the foregoing, it is respectfully submitted that the Supplemental Rule 132 Declaration does demonstrate the unexpected properties of the claimed invention over the prior art and is commensurate in scope with the claimed invention.

Accordingly, favorable reconsideration and allowance is solicited.

Respectfully submitted,

Norihito SHIMONO et al.

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
April 19, 2007